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Treatment of Childhood Hodgkin's Disease With ABVD Without Radiotherapy

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Seventeen previously untreated children with Hodgkin's disease were treated with six courses of the combination adriamycin, bleomycin, vinblastine, and DTIC (ABVD), without radiotherapy, from 1984–1987. In all patients, complete remission was attained. After a median follow-up period of 73.5 months (range 59–98 months), five patients had a relapse after 4, 5, 11, 21, and 34 months, respectively, from attainment of complete remission. In 12 patients with stages I and II, two relapses occurred. Three out of five patients with stage III and stage IV developed a relapse. Based upon these results, we conclude that ABVD might be an appropriate treatment for newly diagnosed children with Hodgkin's disease stages I and II. However, for children with stages III and IV, more intensive treatment is needed. Radio-therapy should be withheld for children with refractory disease, residual disease, or relapse.

Key words: Hodgkin's disease, children, chemotherapy, ABVD

INTRODUCTION

It has been shown that radiotherapy in the treatment regimens for children with Hodgkin's disease may cause serious adverse effects [1]. Therefore, from 1975–1984, 37 children with newly diagnosed Hodgkin's disease were treated in our institute with restricted use of radiotherapy: 21 patients with clinical stages (CS) I–III, having initially "small" lymph node tumors (diameter <4 cm), received six courses of mechlorethamine, vincristine, procarbazine, and prednisone (MOPP), without radiotherapy. Sixteen patients with CS I–III, having "large" lymph node (diameter >4 cm) tumors at diagnosis, also received six MOPP courses, and additionally, radiotherapy, 25 Gy as involved fields on the "large" lymph nodes. With this regimen, 36 children did survive. Relapse occurred in only four patients, two in the chemotherapy group and two in the radiotherapy group. Of these four children, three survived after successful salvage treatment [2].

Based upon these results, the decision was made to treat children with Hodgkin's disease primarily only with chemotherapy, irrespective of the stage of the disease and the size of the lymph node tumors. However, there is growing evidence that alkylating agents such as mechlorethamine and procarbazine cause gonadal damage, not only in adults but also in prepubertal children [3]. Therefore, MOPP was replaced by the combination adriamycin, bleomycin, vinblastine, DTIC (ABVD). In this combination, only DTIC belongs to the category of alkylating drugs.

MATERIALS AND METHODS

Seventeen consecutive and previously untreated children with pathologically proven Hodgkin's disease were involved in this study from September 1984 to December 1987. There were 12 boys and five girls, their ages ranging from 3 to 15 years (median 11.5 years) at diagnosis. Clinical staging included a detailed patient history, physical examination, complete blood count, renal and liver function tests, bone marrow biopsy, chest X-ray, bipedal lymphangiography, and abdominal ultrasound. No child underwent laparotomy with splenectomy. The clinical data of the patients are shown in Table I. There were 10 patients with CS I, two with CS II, three with CS III, and two with CS IV. Six children had B symptoms at diagnosis (unexplained fever, itching, night sweats, weight loss exceeding 10% of normal body weight). One patient (patient K, Table I) had "bulky" mediastinal disease, defined as a mediastinal mass greater than one-third of the thoracic diameter at the level of Th5.

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TABLE I. Clinical Data and Follow-Up of 17 Children with Hodgkin's Disease Initially Treated Only With ABVD

Patient	Age at diagnosis (yr)	Sex	Histology[a]	Clinical stage at diagnosis	B sympt.	Time from diagnosis to CR[b] (mo)	Time from CR to relapse (mo)	Clinical stage of relapse	Therapy of relapse	Subsequent relapses	Survival from diagnosis (mo)	Alive
A	3.8	M	NS	I	−	0	—	—	—	—	98+	Yes
B	11.0	F	NS	I	−	1	34	III-A	3x MOPP-RT (inverted Y 25Gy) −3x MOPP	No	98+	Yes
C	7.0	M	MC	I	+	3	—	—	—	—	97+	Yes
D	5.8	M	MC	I	−	2	—	—	—	—	80+	Yes
E	7.6	M	LP	I	−	1	—	—	—	—	76+	Yes
F	14.4	M	NS	II	−	5	—	—	—	—	75+	Yes
G	14.2	M	NS	I	+	6	—	—	—	—	74+	Yes
H	9.8	F	NS	IV	−	3	21	III-A	6x MOPP	No	74+	Yes
I	11.5	M	LP	I	−	3	11	I-A	6x MOPP	No	73+	Yes
J	14.3	F	MC	I	−	0	—	—	—	—	73+	Yes
K[c]	12.8	M	NS	I	−	[c]	—	—	—	—	71+	Yes
L	15.1	M	NS	II	+	3	—	—	—	—	69+	Yes
M	14.7	M	NS	IV	+	3	5	IV-A	6x MOPP-RT mediast. 25Gy	Yes	67+	Yes
N	13.5	F	NS	III	−	5	4	III-A	8x MOPP-RT (total node irradiation excluding the axillae 11.75Gy)	No	69	No
O	8.3	F	NS	I	−	3	—	—	—	—	64+	Yes
P	9.4	M	NS	III	+	3	—	—	—	—	62+	Yes
Q	15.0	M	NS	III	+	2	—	—	—	—	59+	Yes

[a]NS = nodular sclerosis; MC = mixed cellularity; LP = lymphocytic predominance.
[b]Complete remission.
[c]Time between diagnosis and the attainment of CR could not be determined (see text).

TABLE II. ABVD Regimen

Drugs	Route	Dose	Days
Adriamycin	i.v.	25 mg/m^2	1, 15
Bleomycin	i.v.	10 mg/m^2	1, 15
Vinblastine	i.v.	10 mg/m^2	1, 15
DTIC	i.v.	375 mg/m^2	1, 15

i.v. = intravenous.

Treatment

The ABVD regimen was instituted as the only initial treatment in all 17 patients, irrespective of the stage of the disease and the size of the lymph node tumors. The treatment schedule is shown in Table II. One ABVD course consists of intravenous administration of adriamycin, bleomycin, vinblastine, and DTIC on days 1 and 15. The patients were scheduled to receive six courses during a 6-month period, and in 16 patients these six courses could be given according to the protocol. In one patient (patient K, Table I), the regression of the tumor mass was unsatisfying after three ABVD courses. Therefore, the patient received one additional MOPP course, but, because no further regression of the mass occurred, thoracotomy was performed and a mediastinal tumor was almost completely removed. Histology of this tumor showed a benign thymic cyst without signs of Hodgkin's disease. Therefore, no further treatment was given to this patient.

Surveillance of Toxicity

The toxic effects of adriamycin and bleomycin were assessed after the administration of each course by echocardiography and lung function tests.

RESULTS

Analysis of the data was conducted in January 1993. In 16 children, complete remission (CR) was achieved after the administration of six ABVD courses (range 0–6 courses, median 3 courses). In one child, the time of attainment of CR could not be assessed due to the presence of a benign thymic cyst in the mediastinum, mimicking residual disease (patient K, vide supra).

The actuarial overall survival and disease-free survival (with 95% confidence intervals) at 8 years (median observation time 6 years, range 59 to 98 months) were 92% (92–100) and 71% (53–83), respectively. No patient relapsed during treatment, but after cessation of therapy five patients relapsed after 4, 5, 11, 21, and 34 months from attainment of CR. In 12 patients with CS I and II, two relapses occurred, and three out of five patients with CS III and IV relapsed. Two patients with moderate lymph node swellings at the time of relapse were successfully treated with six MOPP courses without radiotherapy. The remaining three relapsed patients received MOPP with additional radiotherapy. One of these patients, initially having stage IV disease, developed subsequent bone relapses but is currently without signs of disease 2 years after autologous bone marrow transplantation. Another patient (patient N, Table I) died from myelodysplasia after MOPP and total node irradiation. The results are shown in detail in Table I.

In December 1987, the decision was made to stop the accrual to this cohort, because five out of the 17 patients relapsed. We considered this relapse rate to be too high.

Toxicity

Signs of cardiotoxicity were not observed in any of the children after serial echocardiography. In all patients, lung function tests were performed before, during, and after cessation of treatment. In nine patients, no lung toxicity could be demonstrated, but in eight patients a decrease in diffusion capacity of the lungs for carbon monoxide (DLCO) was noted at the end of the treatment period, probably caused by the bolus administration of bleomycin. The decrease was moderate in four patients (10–30%); DLCO was completely normalized in three of them and partially in one. In four other patients who showed a considerable decrease in DLCO (30–60%), its recovery was only partial. There were, however, no *clinical* signs of decreased pulmonary function, and chest X-rays showed no signs of fibrotic lung disease.

DISCUSSION

In children with Hodgkin's disease, concern must be given to the late effects of treatment. The main late effects from radiotherapy include growth disturbance of irradiated tissues, hypofunction of endocrine organs, and early onset vasosclerosis of cardiac blood vessels after mediastinal irradiation [1,4–9]. From the chemotherapeutic agents, the anthracyclines may cause different degrees of cardiomyopathy, the alkylating agents may cause male infertility, and bleomycin may affect the lungs. Combined modality treatment leads to an increased risk of developing secondary cancers [1,8,10].

Malignant lymphomas in childhood are very sensitive to chemotherapy as well as to radiotherapy, and this sensitivity seems higher in children than in adults. In past decades there was a trend to restrict the use of radiotherapy in children with lymphomas, and today non-Hodgkin lymphomas in children are treated only with chemotherapy as first-line treatment. The question should be raised whether childhood Hodgkin's disease also should be treated only with chemotherapy. In a few studies, favourable results have been reported after treatment regimens without radiotherapy [2,11–14]. In these patients, the MOPP combination was used as chemotherapeutic regi-

men. This combination, however, contains two alkylating agents: mechlorethamine and procarbazine. In a fertility study in 20 out of our male patients who were treated with six MOPP courses before puberty, 19 patients were azoospermic or oligospermic after puberty, and all had elevated blood FSH levels [3]. Comparable findings were reported by others [1,15–17].

At present in many treatment regimens for children with Hodgkin's disease, combined modality treatment is given, consisting of moderate doses of radiotherapy, approximately 20 Gy to the involved areas, combined with chemotherapy like MOPP or MOPP variants [5,18,19].

With this policy the sequelae of radiotherapy will be less severe than after 40 Gy extended field radiation, but nevertheless late effects are to be expected, although to a lesser degree. Moreover, the suspicion concerning the development of secondary cancers after combined modality treatment is not expected to disappear after lowering the radiation dose. Because the relapse rate is too high, the results of our pilot study in 17 children with Hodgkin's disease are suboptimal, compared with those after more intensive treatment [5,18,19]. However, 12 of 17 children have obviously been cured without radiotherapy and without the administration of alkylating agents. Ten of these patients had initially stage I or II. From these results one may conclude that ABVD is an attractive first-line regimen for children with stage I or stage II Hodgkin's disease. As has been shown in our previous study with MOPP, with or without radiotherapy, children with stages I or II did better than those with higher stages [2]. This could mean that patients with stages III or IV either need more than six courses of chemotherapy or that radiotherapy should be included.

With every treatment regimen there invariably remains a subgroup of approximately 10% of children, especially in the higher stages, who are refractory or who relapse despite aggressive treatment. Apart from this subgroup, the optimal treatment in the remaining 90% must provide a 100% cure rate without late sequelae. With this in mind, a treatment protocol for children with Hodgkin's disease may be designed in which children with stage I or stage II are treated only with ABVD, according to the therapy scheme mentioned above. Relapses in these patients probably can be salvaged with the noncross-resistant MOPP combination, with or without radiotherapy [20,21]. This is illustrated as well by our (very limited) experience in two patients (Table I, patients H and I). Obviously, children with stage III or IV disease need more intensive treatment than six ABVD courses. In conclusion, we feel that children with Hodgkin's disease should primarily be treated with chemotherapy and that ABVD seems appropriate for patients with stage I or II. Radiotherapy should be withheld for patients with refractory disease, residual disease, or relapse.

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